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Original Research Article

A Single-Center Case Series of Hereditary Ataxia from Gujarat: Clinical and Genetic Data

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ABSTRACT

Background: Hereditary or genetic ataxia is a group of neurodegenerative conditions, characterized by progressive imbalance and ataxia, with convergent clinical profiles. Limited data on the prevalence and subtypes are available from Gujarat due to a lack of an ataxia registry or studies.

Objective: To study clinical and genetic characteristics in patients with hereditary ataxia from Gujarat state.

Material and Methods: This prospective observational study included and evaluated chronic cerebellar ataxia patients with suspected hereditary etiology. Based on the clinical findings, molecular analysis was performed using PCR-based trinucleotide repeat analysis for a single specific genotype, a selected panel, or a broader whole-exome sequencing method.

Results: We identified 65 patients with possible genetic ataxia over 2 years. Forty-nine patients from this subgroup underwent genetic testing and obtained positive results in 29 patients. Spinocerebellar ataxia (SCA) type 2 was the most common type (31%) of Autosomal Dominant ataxia, and Friedreich's ataxia (FA) was the most common Autosomal Recessive ataxia (13.8%). SCA patients had onset in the 2nd decade onwards and had strong positive family history, while FA patients had onset in the 1st decade. Clinical features were overlapping and nonspecific for the subtype of ataxia. Apart from incoordination, the most common clinical findings were eye signs, pyramidal tract involvement and peripheral neuropathy.

Conclusion: Our Gujarat state cohort of hereditary ataxia resembles genotypic and clinical characteristic data from other studies in western India. We noted clinical phenotypic overlap in all subtypes of hereditary ataxia, which calls for molecular genetic testing for diagnosis.

Keywords: Hereditary ataxia, Spinocerebellar ataxia, Friedreich's ataxia, Genetic testing

INTRODUCTION

Ataxia is caused by dysfunction of cerebellum, vestibular system, sensory pathways or any combination of these. Cerebellar ataxia is a common entity worldwide, with aetiologies varying from infection to immune-mediated, nutritional, toxin, structural, and genetic. Hereditary or genetic ataxia is a group of neurodegenerative conditions, characterised by progressive imbalance and ataxia. More than 50 autosomal dominant (AD) and 60 autosomal recessive (AR) ataxia phenotypes have been identified, with definite molecular diagnosis.[1]

Previously, most hereditary cerebellar ataxias were classified based on clinical findings, including cerebellar and other neurological abnormalities, systemic features, and their neuropathological correlates. However, clinical findings in different types of hereditary ataxia were overlapping and nonspecific. [2] Most AD and many AR hereditary ataxias are caused by an expansion of trinucleotide repeats in the genome, coding or non-coding regions. The repeat expansion leads to alterations in proteins,

which exacerbate cerebellar degeneration and cause clinical deficits. Advances in molecular sciences have enabled a more focused classification based on this type of unstable trinucleotide repeat expansion or sequence variant.

Limited data on the prevalence and subtypes of hereditary ataxia are available from the state of Gujarat due to a lack of an ataxia registry or studies. Several studies from different parts of the country have revealed Friedreich's ataxia (FA) as the most common AR and Spinocerebellar ataxia type 2 (SCA2) as the most common AD type of hereditary ataxia. [3,4,5] We attempted to study the common clinical phenotypic presentation of chronic cerebellar ataxia and correlate it with genetic analysis.

MATERIAL AND METHODS

We conducted an observational study of patients with chronic cerebellar ataxia at a tertiary care hospital in Ahmedabad, Gujarat, from October 2017 to January 2020.

Patient selection:

Our patient selection process was meticulous, ensuring that we included only those with a history of more than 3 months and a progressive course, a positive family history, history of consanguinity, and a typical phenotype consistent with described forms of autosomal recessive (AR) or autosomal dominant (AD) ataxia. We excluded acute, sensory and vestibular ataxia and ruled out secondary causes of cerebellar ataxia before inclusion.

Data collection:

A detailed history was taken regarding the onset of symptoms, clinical features, duration, and progression of the illness. Other nervous system involvement was also studied, such as higher mental functions, cranial nerve involvement, motor, sensory, and autonomic system involvement. Family history and history of consanguinity were taken in detail, with a pedigree chart when applicable.

Investigations:

Our investigations were comprehensive, including laboratory tests (hemogram, liver and renal function tests, and lipid profile), MRI of the brain and spine, Thyroid function tests, Vitamin B12 level, and viral markers (HIV, HBsAg, and HCV) in all patients. We also performed other supportive investigations (Ophthalmic Examination, Nerve conduction study (NCS), electromyography (EMG), pure tone audiometry, and other radiological modalities) based on the patient's characteristics.

Specific molecular analysis was done based on clinical history, examination and family history. The PCR amplification method was used to ascertain repeat sizes for SCAs and FA. Initial genetic analysis was conducted for specific SCA subtypes, depending on the clinical phenotype or as a panel, including Trinucleotide repeat analysis for SCA1, 2, 3, 6, and 12 and Friedrich's ataxia. If initial molecular analysis was negative and suspicion of hereditary aetiology was high, further analysis for mitochondrial, other rare subtypes of AD and AR cerebellar ataxia, and/or whole-exome sequencing (WES) was performed in a few selected patients. WES utilises next-generation sequencing technology to analyse the DNA protein-coding region and identify any variations responsible for the disease.

The diagnostic algorithm is illustrated in Fig. 1.

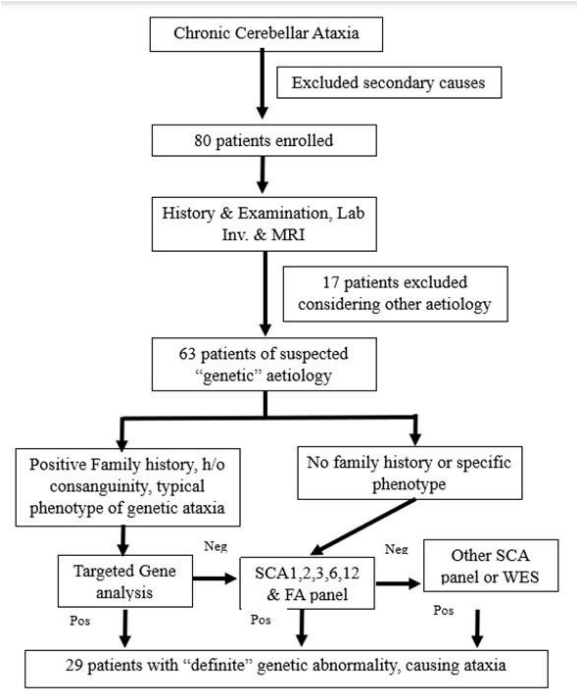

Figure-1: Protocol for evaluation of chronic cerebellar ataxia

(h/o: History of, MRI: Magnetic Resonance Imaging, Neg: Negative, Pos: Positive, SCA: Spinocerebellar ataxia, WES: Whole Exome Sequencing)

RESULTS

Over the 2 years, 80 patients with chronic cerebellar ataxia were enrolled for detailed evaluation in the neurology department at our tertiary care hospital. Fifty-one (63.7%) were male and 29 (36.3%) were female, resulting in a male-to-female ratio of 1.75:1. The mean age of symptom onset was 33.5 years.

After screening and detailed evaluation, we identified 65 patients with possible genetic ataxia, based on their clinical profile, family history, and exclusion of secondary causes. We performed genetic analysis (targeted single-gene, panel, or Whole-Exome Sequencing) in 49 patients from this subgroup and obtained positive results in 29 patients.

Among all genetic ataxias, SCA 2 was the most common, accounting for 31%, followed by SCA 1 at 24.1%. Friedreich's ataxia was the most common autosomal recessive ataxia, accounting for 13.8%. Four patients with mitochondrial gene defects, one patient with SCA 12, and one with L-2-hydroxyglutaric aciduria were diagnosed using specific genetic panels.

The most common presenting symptoms among ataxic patients, apart from progressive incoordination and imbalance, were dysarthria (74.6%), reduced grip (32.6%), and tremors (30.6%). Spinocerebellar ataxia patients in our cohort had onset of symptoms ranging from the 2nd to the 5th decade. The mean duration of illness at presentation was highest in SCA1 (7 years) and lowest in SCA3 (3.3 years). In Friedrich's ataxia subgroup, the mean age of onset was 9.75 years, and the mean duration of illness was 4 years. Positive family history was noted in all patients with SCA1, SCA3, and SCA12, while only 25% of FA patients had a family member with similar symptoms.

Most of our patients have symmetrical and pan-cerebellar syndrome. Eye signs were present in 14 of these 29 subjects, the most common being gaze-evoked nystagmus (41.2%). Slow saccades were seen in two-thirds of SCA2 patients. The most common non-cerebellar feature was pyramidal tract involvement (51.2%), followed by peripheral neuropathy (41.2%). Pyramidal tract involvement was more commonly seen in SCA1 (71.4%) and SCA2 (55.5%). Neuropathy was found most frequently in SCA3 (66.7%) and SCA1 (42.8%).

86.2% of ataxia patients with a genetic aetiology had an abnormal MRI of the brain and/or spinal cord, isolated cerebellar atrophy being the most common finding. The "Hot-cross bun" sign was documented in one patient with SCA1 and SCA2, and brainstem atrophy was noted in one patient with SCA2.

Table 1 outlines the clinical characteristics, radiological features, and other specific findings of individuals with spinocerebellar ataxia.

All four patients with mitochondrial gene defects experienced an onset in the 2nd to 4th decade. Two had progressive vision loss, one had sensorineural hearing loss, and all patients exhibited some other neurological or systemic involvement, including cognitive, pyramidal, extrapyramidal, ophthalmological, or neuromuscular symptoms. A young female with a progressive spinocerebellar phenotype was diagnosed with an L2HGDH gene defect (L-hydroxyglutaric aciduria); she also had cognitive impairment and T2W hyperintensity in the dentate nuclei on MRI.

Table-1: Demographic, clinical and radiological features of Spinocerebellar ataxia (SCA)

	SCA-1	SCA-2	SCA-3	SCA-12
NUMBER	7(35%)	9(45%)	3(15%)	1(5%)
Demographics				
M: F	1.3:1	2:1	2	-
Age of onset (mean & range)	36 (23-55)	35.7 (17-56)	38.6 (34-57)	47
Age at presentation (mean)	42.28	41.22	42	52
Positive Family history	7(100%)	5(55.55%)	3(100%)	1(100%)
CAG repeats (range)	42-56	42-50	79-86	55
Clinical features				
Dysarthria	7(100%)	9(100%)	3(100%)	1(100%)
Tremulousness	7(100%)	9(100%)	3(100%)	1(100%)
Dysdiadochokinesia	7(100%)	9(100%)	3(100%)	1(100%)

Past-pointing	5(71.4%)	7(77.8%)	1(33.3%)	1(100%)
Neuropathy (clinical/physiological)	3(42.8%)	3(33.3%)	2(66.6%)	0
Pyramidal tract involvement	5(71.4%)	5(55.5%)	1(33.3%)	1(100%)
Slow Saccades	1(14.3%)	6(66.7%)	0	0
MRI features				
Cerebellar atrophy	6(85.7%)	6(66.7%)	2(66.7%)	1(100%)
Hot cross bun sign	1(14.3%)	1(11.1%)	0	0
Brainstem atrophy	0	1(11.1%)	0	0
White matter hyperintensities	0	0	1(33.3%)	0

DISCUSSION

We aimed to present the subtypes and characteristics of confirmed cases of genetic ataxia from the state of Gujarat, one of the first reports of this kind from this part of India. Out of 80 screened patients of chronic cerebellar ataxia, 15 patients were excluded based on other diagnostic possibilities or confirmation. Out of 65 suspected genetic ataxia, 49 patients could undergo at least one of the genetic tests (either a single gene or a selected panel), as per the clinical clues. A final confirmed genetic diagnosis could be made in 29 of these forty-nine patients, with a diagnostic yield of 59.2%. The results of molecular testing in suspected cases of genetic ataxia vary from 17% to 36% in various studies, depending on the extent of gene analysis performed. [7,8] An Australian study suggested that a positive family history increases the diagnostic yield of molecular analysis for all types of ataxias. [9] Regional knowledge of genotypes and unbiased sequencing strategies will help improve the diagnosis.

The most common was Spinocerebellar Ataxia type 2 (SCA2), found in nearly one-third of our cohort. Studies from East and North India showed similar results of SCA2, being the most typical subtype for genetic ataxia. [4,10,11] However, reports and case series from other states documented other SCA types in different ethnic populations, such as SCA1 from Tamil Nadu and SCA12 from Northern India. [4,12] Founder effect, i.e., loss of genetic variability in a population established by a small number of individuals, can explain this genetic diversity.

Most patients from our group with Spino-cerebellar ataxia have an age of onset in the 3rd or 4th decade, with a delay of 4 to 7 years before diagnosis. Except for SCA2, positive family history was found in most of the patients. No specific cerebellar signs were pathognomonic for any subtype of spinocerebellar

ataxia. Pyramidal tract involvement was common in SCA1 patients, while SCA3 patients had more polyneuropathy. Similar findings were reported by Pulai et al. from eastern India. [13] Slow saccades were consistently seen in SCA2 patients (66.7%), comparable to other Indian data. One of our SCA1 patients also had this eye finding. Tang et al. detected slow saccades in SCA3 more commonly than in SCA2. [14] Wadia et al. initially described this viscous eye movement as a marker of SCA2, due to selective degeneration of "burst neurons" in the paramedian pontine reticular formation. [15]

Isolated cerebellar atrophy was more common in 6 (85.71%) patients with SCA1, followed by SCA2 and SCA3, consistent with reports from other parts of India. [13,16]

The hot cross bun sign, characterized by cruciform T2W hyperintensities in the pons, was initially thought to be characteristic of 'multisystem atrophy' (MSA) and was noted in one patient with SCA1 and one with SCA2. Khadilkar et al. found a hot cross bun sign in one of their patients who was SCA6 positive.[16] Brainstem atrophy was also documented in one patient of SCA2.

Friedreich's ataxia constituted 13.8 % of all definite genetic ataxia cases. All four patients with Friedreich's ataxia had symptom onset before 25 years of age, with a mean of 9.5 years, and only one had a positive family history. All four patients had areflexia, and three had a CAG repeat of more than 65. Although commonly reported in other Indian studies, we found no patients with Friedreich's ataxia who had either late onset or retained reflexes.[17] Four cases of mitochondrial gene defects were responsible for cerebellar ataxic presentation in this cohort. Singular cases of SCA12 and L2 HD gene abnormality were also reported.

The allele expansion noted in our study ranges from 42 to 56 for SCA1, 42 to 50 for SCA2, and 79 to 86 for SCA3, similar to the molecular data collected by a

central reference laboratory in India. [4] Twenty-one out of 49 patients could not obtain a confirmed clinical genetic diagnosis. This may be attributed to the limited study conducted in some patients, due to cost or refusal, given the unavailability of treatment.

CONCLUSIONS

Phenotypic overlap in all subtypes of genetic ataxia mandates molecular genetic testing to improve the diagnostic process. This reduces the cost of other investigations, helps individuals understand the disease, and aids clinicians in managing and prognosticating. However, the high cost and limited accessibility of genetic testing to many chronic cerebellar ataxia patients in India causes diagnostic errors and the omission of many uncommon variants, specific to the region. The highest number of SCA2 patients in our cohort from Gujarat state signifies genetic similarities from other parts of India. A single-center study and small sample size can limit the generalization of the data.

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